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(P)PARsing Epidermal Development

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Overexpression of PPAR-α, a developmental transcription factor important in epidermal embryogenesis, in basal keratinocytes causes epidermal thinning when activated constitutively during development, but not if activated in adults; and lack of PPAR-α transiently delays stratum corneum formation within a window late in epidermal development (day 18.5 to birth). In contrast, pharmacologic activation of PPAR-α inhibits proliferation and induces differentiation in mouse epidermis regardless of developmental stage. Thus, PPAR-α is an important regulator of epidermal homeostasis.

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Nuclear hormone receptors are transcription factors that regulate the expression of target genes by binding to regulatory DNA sequences and interacting with co-regulatory protein complexes. A large molecular family of these receptors has been identified by homology searches. Soon after the sequences became available, individual receptors were characterized for their tissue distribution, ligand identity, patterns of target gene activation, and interaction with co-regulatory proteins. To better understand their physiological roles, individual receptors were tested in genetic animal models of loss and gain of function.

In this fashion, peroxisome proliferator-activated receptor-α (PPARα) was found to be a nuclear hormone receptor that is activated by fatty acid-derived ligands. Since Issemann and Green cloned mouse PPARα in 1990 and Sher *et al.* cloned its human homologue in 1993 (Issemann and Green, 1990; Sher *et al.*, 1993), several groups have generated mouse models of PPARα deficiency. Such animals displayed abnormal lipid and xenobiotic metabolism in the liver, heart, muscle, and kidney, indicating a role of PPARα in fatty acid oxidation and detoxification of xenobiotic compounds. Although PPARα was originally evaluated for its systemic activities, its expression was soon also noted in skin.

PPARα is present in both epidermis and dermis beginning at day 13.5 of development. Yet shortly after birth it becomes undetectable in the interfollicular epidermis, although expression persists in the hair follicles (Michalik *et al.*, 2001). Injury to adult murine skin, such as hair plucking, induces re-expression of PPARα in the adult interfollicular epidermis, and re-expression can also be observed in the edges of full-thickness wounds. Conversely, in PPARα-deficient mice, the early phase of wound healing is delayed, and this delay is retained when the deficiency is targeted to the epidermis only and not to the dermis (Michalik *et al.*, 2005). In pups lacking PPARα, a delay in stratum corneum formation is observed between day 18.5 of epidermal development and birth (Schmuth *et al.*, 2002), whereas in PPARα-deficient adults, only a modest decrease in the expression of involucrin, loricrin, and filaggrin persists. This indicates that other mediators can compensate for the absence of PPARα; that is, there is redundancy (Komuves *et al.*, 2000).

In this issue, Gonzalez *et al.* (2006) report on the skin phenotype of transgenic mice constitutively overexpressing PPARα in the epidermis. These mice die within 2 days after birth, presumably because of abnormal development of the tongue and mammary gland epithelia; overexpression of PPARα also results in epidermal thinning and sparse fur in these animals, which could contribute to the lethality. Importantly, corresponding to the transient effects of PPARα deficiency on developing epidermis, PPARα overexpression exerts its effects only during a developmental window; that is, after birth it does not cause the abnormalities.

Consequences of a gain of PPARα function have previously been studied using pharmacologic activators. In explants of developing rat epidermis, the expression of proteins required for epidermal differentiation (filaggrin, loricrin, involucrin) was stimulated by the PPARα agonist farnesol (Hanley *et al.*, 1997). In contrast to the VP16PPAR-α bitransgenic mice reported here (Gonzales *et al.*, 2006), there was a concomitant induction of the granular layer. These differences could be explained by differences between *in vitro* and *in vivo* experimental systems and by differences in the timing of the PPARα signal. Nevertheless, in adult mice, pharmacologic activation of PPARα induces epidermal differentiation, inhibits proliferation, and increases

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keratinocyte death. These effects are absent in PPARα knockout mice, which indicates that they are specifically mediated via PPARα (Komuves *et al.*, 2000). Consistent with these findings, Gonzales *et al.* (2006) report here an increase in p21 (Waf1/Cip1) in cultured keratinocytes from 1-day-old neonate mice overexpressing PPARα, which, by causing an arrest in the G1 phase of the cell cycle, may account for the coordinate regulation of proliferation, differentiation, and cell death.

How do these results complement our current knowledge on the transcriptional regulation of epidermal development? Aside from p21, which has been shown to act as a negative regulator of transcription, linking the Notch and Wnt signaling pathways in the control of keratinocyte growth (Devgan *et al.*, 2005), additional transcription factors have been implicated in skin morphogenesis. Whereas LEF-1 and TCF-3 have primarily been investigated for their role in the epidermal stem cell niche (Merrill *et al.*, 2001), the work of Gonzales *et al.* (2006) implies that PPARα is involved in controlling the switch from proliferating basal to differentiating suprabasal keratinocytes. The precise compartmental roles of PPARα remain to be determined, and it is certainly only one of multiple transcription factors involved in controlling epidermal transcription and is likely to interact with additional factors — p63, SP-1, the activator protein-1 transcription factor gene family, c-Myc, RelA, pRb, Klf4, and others (Dai and Segre, 2004). The challenge of future investigations in this field will be to delineate a more complete and possibly quantitative map of interactions among these factors to obtain a better understanding of how epidermal development is orchestrated.

Although it is clear that ligand binding controls the biological activity of PPARα, the specific lipid ligands that PPARα senses physiologically in keratinocytes remain unknown. There is a large number of potential long-chain unsaturated fatty acid ligands, including eicosanoids and leukotrienes, and it is likely that, physiologically, more than one lipid compound is involved. The levels of a variety of ligands, rather than the level of one specific lipid, may be important in determining the activity of the receptor during epidermal development. Because PPARα regulates genes of lipid metabolism, a feedback loop is likely to exist. Additionally, some lipids may be potent activators whereas other lipids may actually behave as antagonists. The phenotype of the PPARα-overexpressing mice generated by the Gonzalez group supports the notion of cross-talk between epidermal lipids and the proteins involved in epidermal development.

Because PPARα can be activated by ligands, the results from the current report provide the rationale for the development of tailored drugs targeting this receptor. In addition to a role in epidermal proliferation and differentiation, PPARα activation has also been shown to be anti-inflammatory, and the delay in wound healing in PPARα-deficient mice has been ascribed to impaired neutrophil and monocyte recruitment during the initial inflammatory phase of wound healing (Michalik *et al.*, 2001). The combination of these effects could be beneficial in the treatment of inflammatory skin disease associated with disturbed epidermal homeostasis. Even though extrapolation from mouse to human is perilous, this research should stimulate translational studies in humans that may lead to new avenues of therapeutic intervention for common dermatologic skin disease.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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